cyclophosphamide 100mg/kg [ideal bw] day -3. Radiation was started at 1200cGy delivered in 150cGy fractions twice a day. Dose of radiation was escalated in increments of 150cGy using cohorts of 3 patients until dose limiting toxicity was reached according to Bearman grading scale. All patients received peripheral stem cells on day 0. GVHD prophylaxis consists of tacrolimus and sirolimus. Patient characteristics are as follows: age 33 yrs(20-54); AML 5, ALL 5, Biphenotypic 2; Disease stage IF 7, 1 RL 5; Donor source sibling 8, matched unrelated 1, mismatched (1 allele) unrelated donor 3; WBC at HCT 1.4(0.2-100.0), blasts in blood 18(0-77%), marrow blasts 30(0-95%). Two patients with no marrow blasts had persistent extramedullary disease at HCT. With a median follow-up for alive patients of 9.2 months (2.9- 27) the overall survival and cumulative incidence of relapse at 6 months are 63% (CI 41%; 78%) and 17% (CI 4%; 50%), respectively. Six patients were treated at 1500cGy without reaching DLT. Four (33%) patients developed acute GVHD, 1 (8%) developed Grade 3-4. The day 30 and day 100 NRM was 0% and 8%, respectively. Most common toxicity was grade 2 stomatitis Causes of death were disease progression 3, GVHD 2 and infection 1.

These preliminary results suggest that 1.) doses of targeted marrow radiation delivered by Tomotherapy can be safely escalated to 1500cGy in combination with etoposide and cyclophosphamide (DLT not reached); and that 2.) a reduction in relapse/progression can be achieved without increasing NRM in this high risk patient population. This observation needs to be confirmed in a larger group of patients.

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EFFECT OF CHROMOSOMAL LESIONS DETECTED BY SNP-ARRAY KARYOTYPING ON SURVIVAL AFTER ALLOGENEIC HCT FOR MDS AND AML

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The prognostic value of chromosomal abnormalities identified by metaphase cytogenetics (MC) in MDS/AML is well-established and has been incorporated into risk stratification schemes. High density single nucleotide polymorphism array (SNP-A) is a karyotyping tool complementary to MC that can detect previously cryptic chromosomal lesions, including acquired somatic uniparental disomy (UPD). We retrospectively analyzed SNP-A results to assess the prognostic relevance of chromosomal abnormalities detected by this method in MDS/AML patients (pts) undergoing allogeneic hematopoietic cell transplantation (HCT).

38 pts who underwent allogeneic HCT between 2004 and 2009 had pre-HCT blood or marrow samples available for SNP-A testing. Cytogenetic analysis was performed on marrow aspirate by standard metaphase karyotyping methods. We performed 250K and 6.0 SNP-A analyses and correlated the results with clinical outcomes. Median pt age at HCT was 56 years (range 20-70). The indication for HCT was either MDS (n = 25, 66%) or AML arising from MDS, and HCT was performed at a median of 5 months from diagnosis (range 3-41). Donor sources were HLA-identical related (21, 55%), unrelated (13, 34%), and cord blood (4, 11%); myeloablative busulfan-based conditioning regimens were used for 24 pts (62%) and reduced intensity fludarabine-based conditioning for the remainder.

Unbalanced chromosomal lesions were detected in 45% of pts by MC and 71% by SNP-A. Acquired somatic UPD, not detectable by MC, was identified in 26% of pts. The presence of SNP-A abnormalities was associated with a trend toward worse overall survival (OS) (16 months vs 45, p = .11). The group of pts < 60 years of age displayed significantly worse OS when SNP-A abnormalities were identified (7 months vs not reached, p = .024). HCT patients with UPD exhibited worse OS (8.8 months vs not reached, p = .016) and relapse-free survival (RFS) (6.6 vs 17.6, p = .018) than those without such lesions. None of the other factors analyzed including the number of prior therapies, HCT donor source, conditioning regimen, or time from diagnosis to HCT was associated with OS or RFS in univariate analyses. We conclude that the detection of new SNP-A abnormalities, particularly UPD, may provide important prognostic information in pts with MDS/AML undergoing HCT and should be further investigated.

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METALLOPORYPHYRIN CONTROLS THE DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIC CELLS

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Backgroud: Heme oxygenase -1 (HO-1) is an inducible cytoprotective molecule, which displays antioxidant, anti-apoptotic and anti-inflammatory effects. HO-1 is well induced in leukemia. However, there is no report about role of HO-1 in leukemia.
Aims: We investigated the involvement of HO-1 in the differentiation of HL-60 cells.
Methods: HO-1 expression was measured by western blot and real-time PCR. Differentiation of HL-60 cells was determined by CD11b expression through flow cytometric analysis.
Results: Dimethylsulfoxide (DMSO), a representative differentiation inducer of HL-60 cells, induced completely decrease HO-1 expression in a time-dependent manner, but increase CD11b, indicating that HO-1 might have negative function in DMSO-induced differentiation of HL-60 cells. Zinc protoporphyrin (ZnPP), a strong inhibitor of HO-1, induced differentiation of HL-60 cells, as evidenced by a marked increase in the expression of CD11b following ZnPP treatment. In contrast, treatment with cobalt protoporphyrin (CoPP), an activator of HO-1, decreased CD11b expression. ZnPP induced down-regulation of HO-1 protein expression in HL-60 cells, while CoPP induced up-regulation. In addition, ZnPP treatment caused a decrease in pRb and cyclin D_1 expression and an increase in p21 and p27 expression.
Conclusions: These results suggest that down-regulation of HO-1 might be necessary for DMSO-induced HL-60 differentiation. This study provides the first evidence that HO-1 plays an important role in DMSO-induced differentiation of HL-60 cells.

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PROGNOSTIC IMPACT OF A MONOSOMAL KARYOTYPE IN PATIENTS WITH ACUTE MYELOID LEUKEMIA UNDERGOING ALLOGENEIC STEM CELL TRANSPLANTATION

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Purpose: Allogeneic stem cell transplantation (alloSCT) is a highly effective treatment for patients (pts) with acute myeloid leukemia (AML). Recently, the presence of a monosomal karyotype was shown to confer to a highly unfavorable prognosis in pts with AML treated with conventional chemotherapy. Therefore, we investigated the prognostic impact of a monosomal karyotype on the outcome of pts with AML following alloSCT.
Patients and Methods: We retrospectively analyzed 153 pts with AML (median age: 45 years, range: 17 – 68 years) who underwent alloSCT in complete remission (CR) at our center between 1994 and 2008. 92 pts (82%) had de novo AML, 27 pts (18%) had therapy-related AML (tAML) or AML evolving from myelodysplastic syndrome. As a stem cell source 131 pts (86%) received peripheral blood stem cells (PBSCs), 22 pts (14%) received bone marrow (BM). Conditioning consisted of standard myeloablative conditioning (MAC) (12 Gy TBI, 2x60mg/kg cyclophosphamide) in 90 pts (59%). 63 pts (41%) received reduced intensity conditioning (RIC) (2x4mg busulfan, 6x30 mg/m2 fludarabine, 4x10mg/kg ATG). 10 pts (7%) had a core-binding factor leukemia (CBF group), 64 pts (41%) were cytogenetically normal (CN group), 19 pts (12%) had an unfavorable risk MK-negative karyotype (MK- group) and 19 pts (12%) had a highly unfavorable MK-positive karyotype (MK+ group) (Breems et al., JCO 26: 4791-4797).
Results: After a median follow-up of 58 months (range: 13-176 months) for the surviving pts, 86 pts (56%) are alive and in CR. Causes of death were relapse in 33 pts (22%) or infections/GvHD in 32 pts (22%). At 3 years projected OS was 55%, whereas the probability of relapse or non-relapse mortality (NRM) was 32% or 22% for the whole cohort. At 3 years patients in the MK+ group had a statistically significantly lower overall survival (OS) of 25% as opposed to 49% (MK- group), 66% (CN group), or 67% (CBF-group)